REMARKS

Claims 1 to 34 are pending.

Claims 10 and 11 were rejected under 35 U.S.C. §112, second paragraph. Claims 10 and 11 have been amended to properly depend from claim 9 for antecedent basis for generation of a model.

Claims 1 to 34 were rejected under 35 U.S.C. §112, first paragraph. The Office Action alleges that the claims contain "subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

The Office Action states that "in order to practice the claimed invention one of skill in the art must be able to conduct an experiment by selecting factors, estimating interactions, assigning probabilities, effecting a combinatorial high throughput screen, and adjusting the probabilities for each interaction according to the results. For the reasons discussed below, this constitutes undue experimentation."

The following paragraphs outline the PTO's arguments with respect to the 35 U.S.C. §112, first paragraph rejection and provide Applicant's response to each argument. Additionally, in accordance with MPEP 713.01, Applicant hereby requests an examiner interview prior to the next office action. Toward that end, Applicant's representative will contact the examiner within a week of filing this amendment to schedule the interview.

A. THE SPECIFICATION TEACHES ONE SKILLED IN THE ART TO SELECT FACTORS, TO ESTIMATE INTERACTION PROBABILITIES FOR AN EXPERIMENT AND TO ADJUST THOSE PROBABILITIES ACCORDING TO RESULTS

The Office Action states that "[t]he specification provides no guidance regarding the factors that should be selected, how estimations are performed, how probabilities are assigned or adjusted." Office Action page 3. Further, the Office Action states that "[b]ase claims 1 and 27 require one to select factors for an experiment. However, there is no

guidance as to what factors should be used or considered for said experiment. Furthermore, there is no guidance as to how to estimate interactions among levels of the factors and then assign a probability value indicating a positive interaction." Office Action page 3.

These statements are incorrect..

First, the "factors" are the factors of an experiment. (Specification paragraphs 0003 and 0008) The term "factor" is known in the experimentation art to mean a "quantity or a variable being studied in an experiment as a possible cause of variation." McGraw-Hill Dictionary of Scientific and Technical Terms, 5th Ed., p 729 (1994). See also, Montgomery, Design and Analysis of Experiments, 5th Ed. (1997, 2001), particularly chapter 1. Paragraph 0011 of the specification states that the factors can be:

> reactant identities and levels and [selection of] process identities and levels and [selection of the] degrees of combination. For example, the experimental factors of the catalyst of a carbonylation reaction can be two different metals and a solvent. Levels of one metal may be Fe, Cu, Ni, Pb, and Re, of another metal may be V, W, Ce, La and Sn and of the solvent may be dimethylformamide (DMFA), dimethylacetamide (DMAA), tetrahydrofuran (THF), diglyme (DiGly) or diethylacetamide (DEAA).

Specification paragraph 0011.

Paragraph 0034 and TABLE 4 show six factor examples of an experiment (TM Type, TM Amount, LM type, LM amount, CS Amount, and CS Type).

The estimations are preformed by "stating the value of a quantity or function based on incomplete data or evidence on a rough or approximate calculation," McGraw-Hill Dictionary of Scientific and Technical Terms, 5th Ed., p 702 (1994). See also, Milliken and Johnson, Analysis of Messy Data; Volume 1: Designed Experiments, 1st. Ed., pp. 104-109 (1992). Paragraph [0008] of the specification teaches a step of estimating interactions among levels of factors of a combinatorial experiment. Paragraph 0011 of the speciation states;

> The method and system can utilize a knowledge matrix as a visual and organizational aid to serve as an adjustable definitional model. The matrix model can include the factors of the experimental space to be investigated. Determination of these factors can require selection of reactant identities and levels and selection of process identities and levels and selection of the degrees of combination. For example, the experimental factors of the catalyst of a carbonylation reaction can be two different metals and a solvent. Levels of one metal may be Fe, Cu, Ni, Pb, and Re, of another metal may be V, W, Ce, La and Sn and of the solvent may be dimethylformamide (DMFA), dimethylacetamide (DMAA), tetrahydrofuran (THF), diglyme (DiGly) or diethylacetamide (DEAA). *The model can be set up originally to represent an estimation of factor level interactions. The estimation can take the form of a probability. The experiment can be conducted and a value of the matrix can be adjusted between each iteration of the experiment to represent a probability change dictated by the experiment results.* (Emphasis added.)

The probabilities are assigned from the estimates. As paragraph 0018 states:

> A method of screening complex catalyzed chemical reactions can be conducted in the FIG. 1 system 10. According to the method, a client and an investigator confer to discuss expectations of the experiment to be conducted in the system 10 and the capability of the system to achieve the expectations. The conference can produce a knowledge matrix comprising the experimental space interactions and an assigned weighting to each interaction that represent a first estimate of a probability that the interaction will be a statistically positive interaction, i.e., that the interaction will be a lead. For example, the probabilities can be high, medium and low probabilities. represented respectively by numerical weighting values. "High, medium and low" mean probabilities that are higher, a medium or lower with respect to one another. When three weighting value probabilities are assigned, the values can be in respective ranges of about 0.6 to about 0.99 for high, about 0.2 to about 0.59 for medium and about 0.01 to about 0.19 for low. Desirably, the respective ranges can be about 0.7 to about 0.9, about 0.2 to about 0.5 and about .05 to about 0.15. The knowledge matrix is an adjustable definitional model that represents the estimated interactions and assigned or adjusted probabilities. The model can be a visual organizational aid or the model can be a virtual construct resident in a computer database.

The EXAMPLE provides literally pages of exemplary processes that serve to instruct one skilled in the art to select factors, estimate interactions and assign a probability value of positive interactions for each of the estimated interactions and to conduct an experiment and adjusting the value.

Quite clearly, one skilled in the experimentation art is enabled by the specification and knowledge in the art to select factors and to estimate interaction probabilities for an experiment and to adjust those probabilities according to results.

B. THE SPECIFICATION TEACHES ONE SKILLED IN THE ART THE STEPS OF A COMBINATORIAL HIGH THROUGHPUT EXPERIMENT

The Office Action also states "[f]urthermore, no active steps are provided that would direct one to conduct an experiment according to the claims" and "[t]he invention is drawn to a method to conduct an experiment. However, no steps are provided to do so" (page 4, d)). The Office Action also argues: "The next requirement is that a combinatorial high throughput screening method be effected. However, there are no guidelines to practice this step. There is no definition of what "effecting" a CHTS method means." Also at page 4, line 16 to page 5,line 2, the Office Action states:

> The skilled petitioner would first turn to the instant specification for guidance to practice methods of conducting a high throughput experiment. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such guidance. The prior art describes numerous techniques available to practice the high throughput technology. However, the specification lacks the guidance to implement such broad claims. Finally, said practitioner would turn to trial and error experimentation to determine the various parameters necessary to practice said invention. Such represents undue experimentation.

These Office Action arguments are incorrect. Paragraphs [0004] to [0006] of the specification state:

> [0004] The steps of a CHTS methodology can be broken down into generic operations including selecting chemicals to be used in an experiment, introducing the chemicals into a formulation system (typically by weighing and dissolving to form stock solutions), combining aliquots of the solutions into formulations or mixtures in a geometrical array (typically by the use of a pipetting robot), processing the array of chemical combinations into products and evaluating the products to produce results.
>
> [0005] Typically, CHTS methodology is characterized by parallel reactions at a micro scale. In one aspect, CHTS can be described as a method comprising (A) an iteration of steps of (i) selecting a set of

> reactants, (ii) reacting the set and (iii) evaluating a set of products of the reacting step and (B) repeating the iteration of steps (i), (ii) and (iii) wherein a successive set of reactants selected for a step (i) is chosen as a result of an evaluating step (iii) of a preceding iteration.
>
> [0006] The study of catalyzed chemical reactions by CHTS involves the investigation of a complex experimental space characterized by multiple qualitative and quantitative factor levels. Typically, the interactions of a catalyzed chemical reaction such as a carbonylation reaction can involve interactions of an order of 6 or 9 or greater. An investigator must carefully set up a CHTS experiment in order to effectively examine such a complex space. Reactant identities and variables, process identities and variables and levels of combinations of factors, must be chosen to define a space that will provide meaningful results.

The term "effecting" is the gerund of the verb, "effect," meaning "to cause to come into being,... to bring about." Merriam Webster's Collegiate Dictionary, 10th Ed., p. 367 (1993).

A quick search of the PTO patent data base reveals approximately 500 pre August 2001 patents that teach combinatorial processes.

Numerous literature references teach combinatorial processes. For example, see Terrett, Combinatorial Chemistry, Oxford University Press (1998).

FIG. 1 illustrates a CHTS experiment. Paragraphs [0017] and [0019] through [0027] disclose details of the conduct of an experiment according to the claims. The EXAMPLE provides literally pages of exemplary processes that serve to instruct one skilled in the art to conduct an experiment according to the claims. Quite clearly, one skilled in the experimentation art is enabled by the specification and knowledge in the art to conduct an experiment according to the claims. This basis of the rejection should be withdrawn.

C. THE SPECIFICATION TEACHES ONE SKILLED IN THE ART TO DEFINE AN EXPERIMENTAL SPACE

The Office Action argues that "the claims require an experimental space, however, the specification does not set forth any steps or methods to ascertain or set up an experimental space." This argument is incorrect. Defining an experimental space is

taught in the specification paragraphs [0002], [0003], [0015] and [0019]. Paragraph [0018] of the specification teaches:

> [0011] In one embodiment, the invention provides a method and system to permit a client and an investigator to confer to develop an experiment definition for a CHTS experiment. The method and system can utilize a knowledge matrix as a visual and organizational aid to serve as an adjustable definitional model. The matrix model can include the factors of the experimental space to be investigated. Determination of these factors can require selection of reactant identities and levels and selection of process identities and levels and selection of the degrees of combination. For example, the experimental factors of the catalyst of a carbonylation reaction can be two different metals and a solvent. Levels of one metal may be Fe, Cu, Ni, Pb, and Re, of another metal may be V, W, Ce, La and Sn and of the solvent may be dimethylformamide (DMFA), dimethylacetamide (DMAA), tetrahydrofuran (THF), diglyme (DiGly) or diethylacetamide (DEAA).

And, paragraphs [0020] to [0027] teach:

> [0020] In one embodiment, the invention is applied to study a process for preparing diaryl carbonates. Diaryl carbonates such as diphenyl carbonate can be prepared by reaction of hydroxyaromatic compounds such as phenol with oxygen and carbon monoxide in the presence of a catalyst composition comprising a Group VIIIB metal such as palladium or a compound thereof, a bromide source such as a quaternary ammonium or hexaalkylguanidinium bromide and a polyaniline in partially oxidized and partially reduced form. The invention can be applied to screen for a catalyst to prepare a diaryl carbonate by carbonylation.
>
> [0021] Various methods for the preparation of diaryl carbonates by a carbonylation reaction of hydroxyaromatic compounds with carbon monoxide and oxygen have been disclosed. The carbonylation reaction requires a rather complex catalyst. Reference is made, for example, to Chaudhari et al., U.S. Pat. 5,917,077. The catalyst compositions described therein comprise a Group VIIIB metal (i.e., a metal selected from the group consisting of ruthenium, rhodium, palladium, osmium, iridium and platinum) or a complex thereof.
>
> [0022] The catalyst material also includes a bromide source. This may be a quaternary ammonium or quaternary phosphonium bromide or a hexaalkylguanidinium bromide. The guanidinium salts are often preferred; they include the ∀, T-bis(pentaalkylguanidinium)alkane salts. Salts in which the alkyl groups contain 2-6 carbon atoms and especially

tetra-n-butylammonium bromide and hexaethylguanidinium bromide are particularly preferred.

[0023] Other catalytic constituents are necessary in accordance with Chaudhari et al. The constituents include inorganic cocatalysts, typically complexes of cobalt(II) salts with organic compounds capable of forming complexes, especially pentadentate complexes. Illustrative organic compounds of this type are nitrogen-heterocyclic compounds including pyridines, bipyridines, terpyridines, quinolines, isoquinolines and biquinolines; aliphatic polyamines such as ethylenediamine and tetraalkylethylenediamines; crown ethers; aromatic or aliphatic amine ethers such as cryptanes; and Schiff bases. The especially preferred inorganic cocatalyst in many instances is a cobalt(II) complex with bis-3-(salicylalamino)propylmethylamine.

[0024] Organic cocatalysts may be present. These cocatalysts include various terpyridine, phenanthroline, quinoline and isoquinoline compounds including 2,2':6',2"-terpyridine, 4-methylthio-2,2':6',2"-terpyridine and 2,2':6',2"-terpyridine N-oxide,1,10-phenanthroline, 2,4,7,8-tetramethyl-1,10-phenanthroline, 4,7-diphenyl-1,10, phenanthroline and 3,4,7,8-tetramethy-1,10-phenanthroline. The terpyridines and especially 2,2':6',2"-terpyridine are preferred.

[0025] Another catalyst constituent is a polyaniline in partially oxidized and partially reduced form.

[0026] Any hydroxyaromatic compound may be employed. Monohydroxyaromatic compounds, such as phenol, the cresols, the xylenols and p-cumylphenol are preferred with phenol being most preferred. The method may be employed with dihydroxyaromatic compounds such as resorcinol, hydroquinone and 2,2-bis(4-hydroxyphenyl)propane or "bisphenol A," whereupon the products are polycarbonates.

[0027] Other reagents in the carbonylation process are oxygen and carbon monoxide, which react with the phenol to form the desired diaryl carbonate.

The EXAMPLE provides literally pages of exemplary processes that serve to instruct one skilled in the art to define an experimental space.

The Office Action argues that "[t]he specification provides a working example of a non-defined chemical space (Table I and Table II). However, this does not provide a means for which to practice said invention." Applicant fails to understand this argument. First, the chemical space is defined, not "non-defined" in TABLE 1 and in TABLE 2.

See also, TABLE 3 and TABLE 4. Second, Applicant knows of no patent law requirement to "provide a means for which to practice the invention." The PTO is respectfully requested to withdraw this basis of rejection or to explain what it means by this statement in a non-final office action.

Quite clearly, one skilled in the experimentation art is enabled by the specification and knowledge in the art to define an experimental space according to the claims. This basis of the rejection should be withdrawn.

D. THE SPECIFICATION TEACHES ONE SKILLED IN THE ART HOW TO ADJUST PROBABILITIES

The Office Action states:

> Finally, probabilities should be adjusted for the interactions. How are these to be adjusted? Furthermore, what does the adjustment ultimately achieve?

The term "adjusted value" means "a value of a quantity derived from observed data by some orderly process, which eliminates discrepancies arising from errors in those data." McGraw-Hill Dictionary of Scientific and Technical Terms, 5th Ed., p 37 (1994). The term "adjusting the probabilities for each interaction according to results of the CHTS method" as used in the specification and claims, means that the assigned probability is changed to a quantity derived from the observed results of the CHTS method to eliminate discrepancies in the assigned probability. Adjusting probabilities is taught in the specification paragraphs [0009], [0011] and [0018]. Paragraphs [0035] and [0036] of the specification teach:

> [0035]The client and the investigator observe the rows of TABLE 5 that contain interactions. In the TABLE 5, only three of the interactions, marked **, show very strong evidence of statistical significance ($P<0.001$), and one, marked *, shows moderately strong evidence ($P<0.02$). Two show weak evidence ($P\sim0.05$). The rest show no evidence of interaction. The client and the investigator then adjust the weighted probabilities in the computer matrix according to the observed statistically significant results. The probabilities are increased for all the strong interactions and decreased for weak interactions. The following algorithm is used as illustrated in TABLE 6: (1) Very strong interaction: increase the matrix amount by half a distance to 1.0. (2) Moderately strong

interaction: increase by .25 the distance to 1.0. (3) Weak evidence: no change. (4) No evidence: decrease by half the distance to zero.

TABLE 6

	TM type	TM Amount	LM type	LM Amount	CS Type	CS Amount
TM type	1	0.8+.1	0.3+.35	0.3-.15	0.3	0.3-.15
TM Amount	0.8+.1	1	0.3+.35	0.1-.05	0.3-.15	0.1-.05
LM type	0.3+.35	0.3+.35	1	0.8	0.3-.15	0.1-.05
LM Amount	0.3-.15	0.1-.05	0.8	1	0.1-.05	0.1+.225
CS Type	0.3	0.3-.15	0.3-.15	0.1-.05	1	0.8-0.4
CS Amount	0.3-.15	0.1-.05	0.1-.05	0.1+.225	0.8-0.4	1

[0036] The revisions shown to TABLE 6, result in TABLE 7.

TABLE 7

	TM type	TM Amount	LM type	LM Amount	CS Type	CS Amount
TM type	1	.9	.65	.15	0.3	.15
TM Amount	.9	1	.65	.05	.15	.05
LM type	.65	.65	1	.8	.15	.05
LM Amount	.15	.05	.8	1	.05	.325
CS Type	0.3	.16	.15	.05	1	.4
CS Amount	.15	.05	.05	.325	.4	1

The EXAMPLE provides literally pages of exemplary processes that serve to instruct one skilled in the art to adjust probabilities according to the claims. Quite clearly, one skilled in the experimentation art is enabled by the specification and knowledge in the art to adjust probabilities according to the claims. This basis of the

rejection should be withdrawn.

E. THE CLAIM FORMAT IS CORRECT

The Office Action states;

> The preamble requires the implementation of a method to conduct an experiment. No experiment is conducted in the steps of base claim 1.

Applicant does not understand this basis of rejection. First, the preamble of claim 1 does not require "the implementation of a method to conduct an experiment." The preamble of claim 1 states that what is claimed is "[a] method to conduct an experiment." Second, 35 U.S.C. §112, first paragraph states that "the specification shall contain a written description of the invention, and of the manner and process of making and using it ... to enable any person skilled in the art.. to make and use the same...." The PTO is specifically requested to explain in what manner 35 U.S.C. §112, first paragraph requires recitation of conducting an experiment in the steps of a claim. The PTO is requested to withdraw this basis of rejection or to provide this explanation in a non-final office action.

F. THE INVENTION IS NEW AND UNOBVIOUS

The Office Action states:

> It would have been well known in the art that systems to conduct combinatorial experiments through high throughput were available. For instance, Chose et al. (Journal of Combinatorial Chemistry (1999) Vol.1:55-68) describe approaches to designing combinatorial libraries for drug discovery. This approach utilizes molecular databases, physiochemical properties of molecules, profiling, comparisons and analysis of chemical functionalities. Numerous other systems and techniques such as QSAR, COMMA, and COMFA methods are well known in the art. However, absent specific, illustrative guidance in the specification, the instant claims are not enabled. There is no guidance on how to perform the selecting, estimating, assigning, and adjusting steps.

Office Action page 4, lines 3 to 11.

Again, Applicant fails to understand the rejection. Again, 35 U.S.C. §112, first paragraph states that "the specification shall contain a written description of the invention, and of the manner and process of making and using it ... to enable any person

skilled in the art.. to make and use the same...." The PTO is specifically requested to explain in what manner, the statement of the Office Action page 4, lines 3 to 11 relates to the requirements of 35 U.S.C. §112, first paragraph. The PTO is requested to withdraw this basis of rejection or to provide this explanation in a non-final office action.

Furthermore, Applicant vigorously disputes and traverses the PTO Office Action page 4, lines 3 to 11 assertions. See MPEP §2144.03. If this paragraph is intended to be a 35 U.S.C. §102 or 35 U.S.C. §103(a) based rejection, then the PTO is requested to withdraw the rejection or to properly apply such a rejection in a non-final office action.

G. 35 U.S.C. §112, FIRST PARAGRAPH DOES NOT PROHIBIT BROAD CLAIMS

The Office Action states:

> The claims are broad because they are not limited to any particular factors, values, screening methods, adjustments. While some claims are directed to factors such as catalyst metals (claim 21, for example), there are still no steps that would explain or define how to estimate interactions between those given factors.

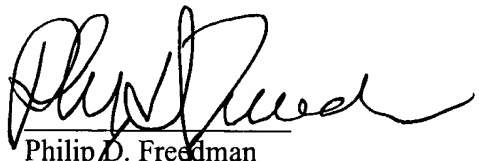
Office action page 4, lines 12 to 15.

Again, Applicant fails to understand the rejection. Again, 35 U.S.C. §112, first paragraph states that "the specification shall contain a written description of the invention, and of the manner and process of making and using it ... to enable any person skilled in the art.. to make and use the same...." The PTO is specifically requested to explain in what manner, broad claims relate to the requirements of 35 U.S.C. §112, first paragraph. The PTO is requested to withdraw this basis of rejection or to provide this explanation in a non-final office action.

In view of the foregoing amendments and remarks, it is respectfully submitted that claims 1 to 34 are allowable. Reconsideration and allowance are requested.

Should the Examiner believe that any further action is necessary in order to place this application in condition for allowance, he is requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Philip D. Freedman
Reg. No. 24,163
Philip D. Freedman PC
Customer Number 25101
6000 Wescott Hills Way
Alexandria, Virginia 22315-4747
(703) 313-0171
Fax: (703) 313-9322
Email: tekesq@tekesq.com

Alexandria, Virginia
Mar. 31, 2003